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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/512,568	02/24/2000	Mich B. Hein	TSRI-184.2Con3	5810
30542	7590	07/27/2004	EXAMINER	
FOLEY & LARDNER P.O. BOX 80278 SAN DIEGO, CA 92138-0278			COLLINS, CYNTHIA E	
			ART UNIT	PAPER NUMBER
			1638	
DATE MAILED: 07/27/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/512,568

Applicant(s)

HEIN ET AL.

Examiner

Cynthia Collins

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21,24-40,43,50,54-63,69-80 and 101-106 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 43, 50, 54-63, 69-79 is/are allowed.
- 6) ☒ Claim(s) 21,24-27,29,30,39,40,80 and 101-106 is/are rejected.
- 7) ☒ Claim(s) 28 and 31-38 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

The Amendment filed March 15, 2004 has been entered.

Claims 1-20, 22-23, 41-42, 45-49, 51-53, 64-68 and 81-100 are cancelled.

Claims 21, 26 and 63 are presently amended.

Claims 103-106 are newly added.

Claims 21, 24-40, 43, 50, 54-63, 69-80 and 101-106 are pending and are examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Inventorship

Receipt is acknowledged of the statement requesting that Julian K-C Ma be deleted as a named inventor which was filed with the Continued Prosecution Application (CPA) on March 1, 2002. The inventorship has been corrected as requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 24-27, 29-30, 39-40, 78, 80 and 101 remain rejected, and newly added claims 103-106 are rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

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specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the office action mailed September 15, 2003.

Applicant's arguments filed March 15, 2004, have been fully considered but they are not persuasive.

Applicants first point out that the inventors' original success expressing the 6D4 IgG class catalytic antibody in plants led directly to the successful expression in plants of a complete IgA secretory immunoglobulin, a complex multisubunit protein requiring the assembly of ten subunits representing four different polypeptides (reply page 10). Applicants also point to Example 15 of the patent application which describes the process used for expressing secretory IgA in plants (reply page 10). Applicants argue that one skilled in the art would acknowledge that the application provides substantial evidence supporting the ability of plant cells to assemble complex multimeric proteins, and Applicants further point out that nucleotide sequences encoding a wide array of multimeric proteins are publicly available (reply page 10). Applicants additionally note that the inventors have demonstrated highly successful assembly of two very different type of immunoglobulins, one a tetrameric (4) multichain immunoglobulin formed from two polypeptides and the other a decameric (10) multi-chain immunoglobulin formed from four different polypeptides (reply page 11). Applicants argue that one skilled in the art would acknowledge that successful assembly of these two different immunoglobulins predicts success not only for immunoglobulins but also for other members of immunoglobulin gene superfamily (reply page 11). Applicants further argue that their success in obtaining assembly of a very complex multimeric protein such as secretory IgA, which requires assembly of both

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immunoglobulin and nonimmunoglobulin gene superfamily polypeptides, is evidence of their possession of multimeric proteins beyond the immunoglobulin gene superfamily, and that Applicants are entitled to a broad scope even though only a small portion of the claimed genus has been reduced to practice (reply pages 11-12).

The rejection is maintained because Applicants have not described a representative number of species falling within the scope of the claimed genus, nor the structural features unique to the genus. With the exception of newly added claim 103, the rejected claims are not limited to plant cells comprising and expressing sequences encoding any specific class of multimeric proteins, such that the genus of expressed sequences encompasses encoding any multimeric proteins of any size and composition and function obtained from any species of living organism. The Office maintains that the description of plant cells comprising and expressing sequences encoding multimeric immunoglobulin proteins does not constitute a representative number of species falling within the scope of the claimed genus cells that comprise and express sequences encoding any multimeric proteins of any size and composition and function obtained from any species of living organism, nor the structural features unique to the genus that allow for expression and assembly of the multimeric proteins. With respect to newly added claim 103, the Office maintains that the description of plant cells comprising and expressing sequences encoding multimeric immunoglobulin proteins does not constitute a representative number of species falling within the scope of the claimed genus cells that comprise and express sequences encoding all multimeric proteins belonging to the immunoglobulin gene superfamily, nor the structural features unique to the genus that allow for expression and assembly of these multimeric proteins, as the immunoglobulin gene superfamily is known to encode a diverse array

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of multimeric proteins, including T cell receptor complex proteins, major histocompatibility complex antigens, β_2 -m associated antigens, T lymphocyte antigens, haemopoietic/endothelium antigens, brain/lymphoid antigens, immunoglobulin receptors, neural molecules, tumor antigens, growth factor receptors, and non-cell surface molecules, in addition to immunoglobulins (see specification Table A pages 12-13).

Claims 21, 24-27, 29-30, 39-40, 80 and 101 remain rejected, and newly added claims 101-106 are rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the exemplified plant cells containing antigen-specific antibodies, does not reasonably provide enablement for plant cells containing nucleotide sequences encoding any non-plant biologically functional multimeric protein, assembly of any two polypeptides to form a multimeric protein, or for transgenic plants in which any non-plant biologically functional multimeric protein is present at a level of at least 56 ng/mg of total protein in its extract. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record set forth in the office action mailed September 15, 2003.

Applicant's arguments filed March 15, 2004, have been fully considered but they are not fully persuasive.

Applicants argue that the rejection applies a view of the field that existed prior to but not after the inventors' discovery that plants could be used to express not only heteromultimeric non-plant proteins, but even very specialized such proteins that have no counterpart in plants. Applicants point out that in particular, the inventors achieved assembly of heteromultimeric

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proteins in plants using plant transformation methods that were then in common use Applicants argue that the evidence of record supports that Applicants' success enables the expression of a wide variety of non-plant proteins in plants. Applicants further point out that the identity of subunits is determined by the cells which naturally produce multimeric proteins, and that different levels of expression, if required, are readily achieved in plant cells using different promoters that are known in the art. Applicants further argue that in view of their successful expression and assembly of secretory IgA in plant cells, the instant rejection is flawed because it is based on concerns about non-plant protein expression in plants that have been eliminated or reduced following the work of the inventors. Applicants also point out that the claims do not require 100% assembly of multimeric protein, or even assembly at levels similar to those of cells that natively express the multimer. (reply pages 13-14).

The rejection is not wholly predicated on the expression of non-plant polypeptides per se in plant cells, but is substantially predicated on the unpredictability of non-plant polypeptides assembling to form multimers in plant cells (or any cells) upon their expression, which unpredictability the Office maintains has not been eliminated or reduced by Applicants' successful expression and assembly of a single class of multimeric proteins (immunoglobulins) in plant cells. While the identity of subunits is determined by the cells which naturally produce multimeric proteins, and while different levels of expression, if required, may be achieved in plant cells using different promoters that are known in the art, the Office maintains that the specification does not provide sufficient guidance with respect to which unspecified subunits to express, and at which level, in order to achieve the assembly of a particular multimeric protein in

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a plant cell. In this regard Applicant has not provided guidance directed to the expression and assembly of any nonimmunoglobulin multimeric protein at any detectable level in a plant cell.

Applicants further argue that the references cited by the Examiner do not provide evidence of the nonenablement of the invention. In particular, Applicants argue that Lippencott-Schwartz et al. does not provide evidence of the nonenablement of the invention, as Lippencott-Schwartz et al. do not teach that altering the relative levels of subunit expression will not result in subunit assembly (reply page 14).

The Office maintains that Lippencott-Schwartz et al. provide evidence of the nonenablement of the invention in so far as it was cited in order to illustrate the general inference that since multimeric protein subunits are known to accumulate at different levels under native conditions for some multimeric, the relative levels of subunit expression may play a role in subunit assembly, and in so far as the claims do not specify the nature of the multimeric protein to be assembled upon the expression of its subunits in plant cells.

Applicants also argue that Waldman et al. does not provide evidence of the nonenablement of the invention, as Waldman et al. do not teach that the delta chain would not associate with the beta and gamma sodium channel chains in plant cells as it did in frog oocytes. (reply pages 14-15).

The Office maintains that Waldman et al. provide evidence of the nonenablement of the invention in so far as it was cited in order to illustrate the general principal that since proper multimer assembly may require the expression and/or presence of each different polypeptide in the same cell or cellular compartment, guidance with respect to which polypeptides need be

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expressed and present may be required to enable intracellular multimer assembly, and in so far as the claims do not specify the nature of the multimeric protein to be assembled upon the expression of its subunits in plant cells.

Applicants additionally argue that Bonifacino et al. does not provide evidence of the nonenablement of the invention, as the variable at issue in Bonifacino et al. (degradation of one subunit absent sufficient quantities of other subunits) has been overcome by Applicants in that immunoglobulin heavy chains are also subject to this phenomenon, and as one skilled in the art need not understand this phenomenon to practice the claimed invention . (reply page 15).

The Office maintains that Bonifacino et al. provide evidence of the nonenablement of the invention in so far as it was cited in order to illustrate the general principal that since proper multimer assembly may require the presence of all multimer subunits, guidance with respect to whether all polypeptides need be present simultaneously may be required to enable intracellular multimer assembly, and in so far as the claims do not specify the nature of the multimeric protein to be assembled upon the expression of its subunits in plant cells.

Applicants further argue that Yu et al. does not provide evidence of the nonenablement of the invention, as the requirement for host cofactors would be known or readily determined on a case-by case-basis without undue experimentation depending on the multimer (reply page 15-16).

The Office maintains that Yu et al. provide evidence of the nonenablement of the invention in so far as it was cited in order to illustrate the general principal that since proper multimer assembly may require the presence of host cofactors, some guidance with respect to which cofactors are needed may be required to enable intracellular multimer assembly, and in so

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far as the claims do not specify the nature of the multimeric protein to be assembled upon the expression of its subunits in plant cells.

Claim 21, and claims 24-27, 29-30 and 39-40 dependent thereon, remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of “biologically functional”, for the reasons of record set forth in the office action mailed September 15, 2003.

Applicant's arguments filed March 15, 2004, have been fully considered but they are not persuasive.

Applicant argues that the Examiner's rationale for the rejection does not indicate why this term would be unclear. Applicant points out that one skilled in the art knows that all proteins have one or more biological functions, which is a biological activity that the protein performs when its expressed in its native state. Applicant also points out that the specification teaches the well known fact that the biological activity of multimeric proteins depends on proper assembly of the subunits. Applicant additionally points out that it would be impossible for Applicants to recite all possible biological activities for each and every non-plant multimeric protein falling under the claim. Applicant submits that the claim is reasonably clear because one skilled in the art would understand that that phrase biological function is a reference to a biological function of the multimeric protein that is inherent in the protein when properly assembled. (reply page 17).

The rejection is maintained because it is unclear in what way the multimeric protein is “biologically functional”. It is unclear because the identity of the multimer is not specified, and because any protein would be presumed to have a “biologic” function of some kind. As Applicant points out, all proteins are presumed to have one or more biological functions, which

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is a biological activity that the protein performs when it is expressed in its native state. The biological activity could be interpreted as being the effect(s) that the protein has on the biological system (native or heterologous) in which it is expressed, which effect(s) would vary depending on the nature of the particular protein expressed and the nature of the biological system in which it is expressed. Alternatively, the biological activity could be interpreted as being one or more of the specific activities (enzymatic activity, binding activity, etc.) that the protein itself inherently exhibits as a consequence of its structure, which specific activities would vary depending on the nature of the particular protein. Because neither the identity of the multimeric protein nor the nature of the biological function are referred to in the claim, the use of the phrase “biologically functional” alone to modify an unidentified multimeric protein renders the claim indefinite.

Allowable Subject Matter

Claims 28 and 31-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

~~THIS ACTION IS MADE FINAL.~~ Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

Claims 43, 50, 54-63, 69-79 are allowed.

Claims 28 and 31-38 are objected to.

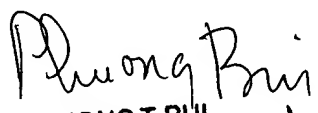
Claims 21, 24-27, 29-30, 39-40, 80 and 101-106 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins


PHUONG T. BUI
PRIMARY EXAMINER 7/12/04